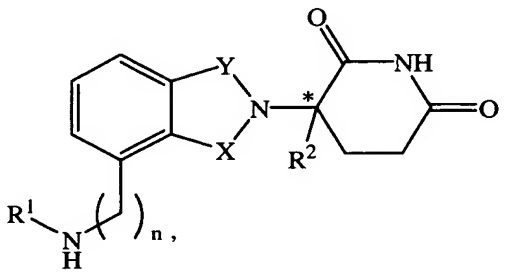
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A compound of the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof~~, wherein:

one of X and Y is C=O and the other is CH_2 or C=O;

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H, F, benzyl, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$alkynyl, with the proviso that when n is 0, R^2 is H or $(C_1$-$C_4)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–C(O)O–R^5 or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R^1 is not H.

2. (Currently Amended) The compound of claim 1, wherein the compound is the R-enantiomer or substantially [R] pure R-form.

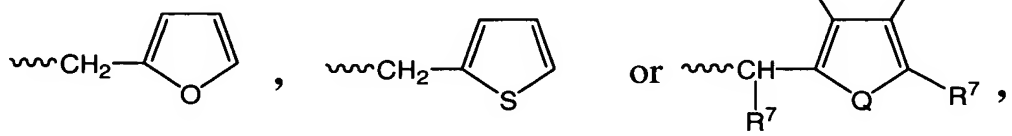
3. (Currently Amended) The compound of claim 1, wherein the compound is the S-enantiomer or substantially [S] pure S-form.

4. (Original) The compound of claim 1, wherein the compound is a racemic mixture.

5. (Original) The compound of claim 1, wherein the enantiomeric excess is about 90% ee or more.

6. (Original) The compound of claim 1, wherein R^2 is H or $(C_1$-$C_4)$alkyl

7. (Original) A compound of claim 1, wherein R^1 is H, $(C_1$-$C_4)$alkyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or

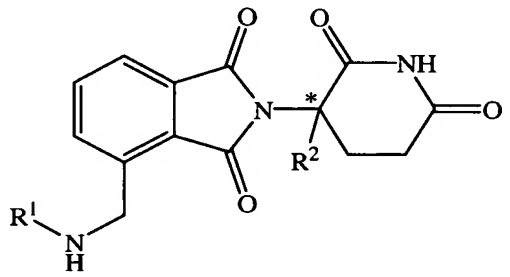


wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, halogen, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–C(O)OR^5, $(C_1–C_8)$alkyl–O(CO)R^5, or C(O)OR^5, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

8. (Original) A compound of claim 1, wherein R^1 is $C(O)R^3$.

9. (Original) A compound of claim 1, wherein R^1 is $C(O)OR^4$.

10. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1–C_8)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

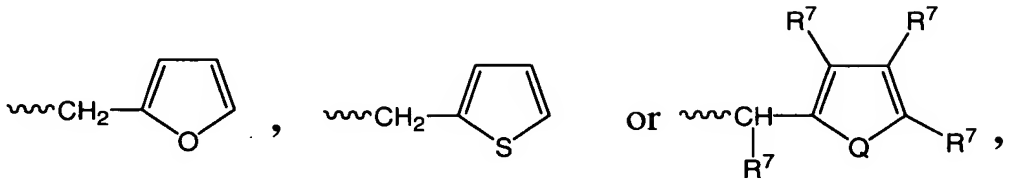
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

11. (Original) A compound of claim 10, wherein R^1 is H, $(C_1$-$C_4)$alkyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or

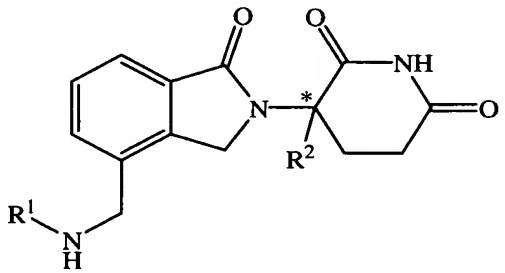


wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1$–$C_8)$alkyl, $(C_3$–$C_7)$cycloalkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$alkynyl, benzyl, aryl, halogen, $(C_0$–$C_4)$alkyl–$(C_1$–$C_6)$heterocycloalkyl, $(C_0$–$C_4)$alkyl–$(C_2$–$C_5)$heteroaryl, $(C_0$–$C_8)$alkyl–$N(R^6)_2$, $(C_1$–$C_8)$alkyl–OR^5, $(C_1$–$C_8)$alkyl–$C(O)OR^5$, $(C_1$–$C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

12. (Original) A compound of claim 10, wherein R^1 is $C(O)R^3$.

13. (Original) A compound of claim 10, wherein R^1 is $C(O)OR^4$.

14. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is H, $(C_1$–$C_8)$alkyl, $(C_3$–$C_7)$cycloalkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$alkynyl, benzyl, aryl, $(C_0$–$C_4)$alkyl–$(C_1$–$C_6)$heterocycloalkyl, $(C_0$–$C_4)$alkyl–$(C_2$–$C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$,

$C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1–C_8)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

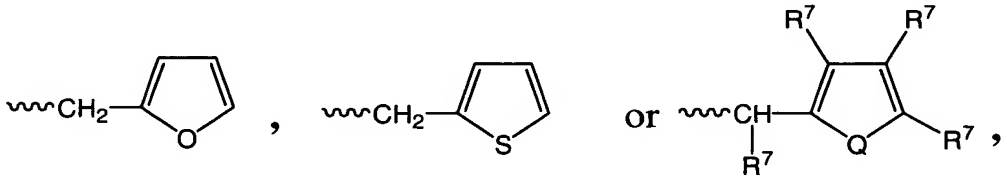
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

15. (Original) A compound of claim 14, wherein R^1 is H, $(C_1$-$C_4)$alkyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or

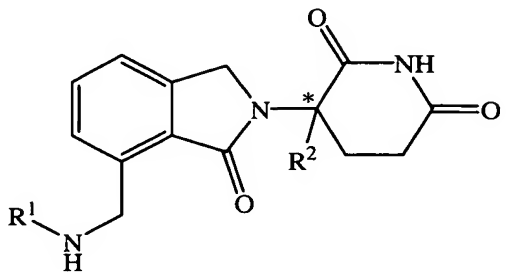


wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, halogen, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

16. (Original) A compound of claim 14, wherein R^1 is $C(O)R^3$.

17. (Original) A compound of claim 14, wherein R^1 is $C(O)OR^4$.

18. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1–C_8)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

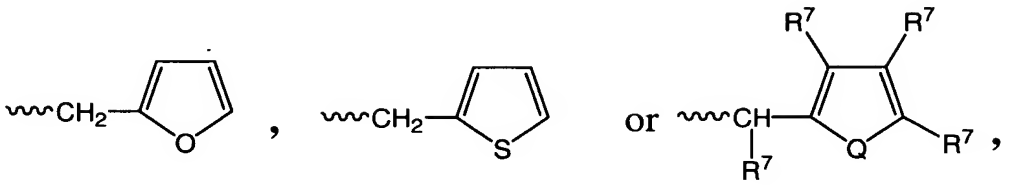
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

19. (Original) A compound of claim 18, wherein R^1 is H, $(C_1$-$C_4)$alkyl, CH_2OCH_3, $CH_2CH_2OCH_3$ or

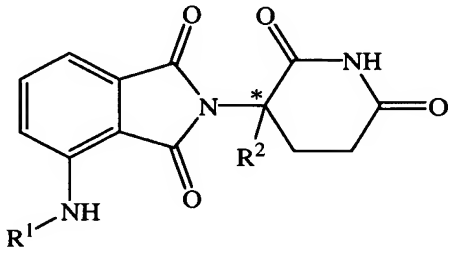


wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1$–$C_8)$alkyl, $(C_3$–$C_7)$cycloalkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$alkynyl, benzyl, aryl, halogen, $(C_0$–$C_4)$alkyl–$(C_1$–$C_6)$heterocycloalkyl, $(C_0$–$C_4)$alkyl–$(C_2$–$C_5)$heteroaryl, $(C_0$–$C_8)$alkyl–$N(R^6)_2$, $(C_1$–$C_8)$alkyl–OR^5, $(C_1$–$C_8)$alkyl–$C(O)OR^5$, $(C_1$–$C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

20. (Original) A compound of claim 18, wherein R^1 is $C(O)R^3$.

21. (Original) A compound of claim 18, wherein R^1 is $C(O)OR^4$.

22. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is ~~H,~~ $(C_1$–$C_8)$alkyl, $(C_3$–$C_7)$cycloalkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$alkynyl, benzyl, aryl, $(C_0$–$C_4)$alkyl–$(C_1$–$C_6)$heterocycloalkyl, $(C_0$–$C_4)$alkyl–$(C_2$–$C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1$–$C_8)$alkyl–$N(R^6)_2$, $(C_1$–$C_8)$alkyl–OR^5, $(C_1$–$C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1$–$C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1$-$C_4)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

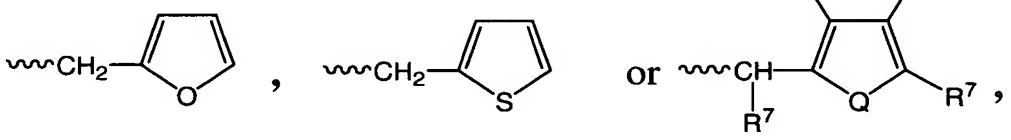
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

23. (Original) A compound of claim 22, wherein R^1 is $(C_1–C_8)$alkyl, benzyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or



wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, halogen, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

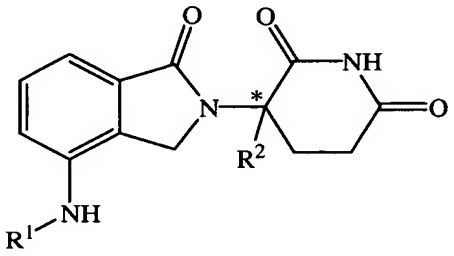
24. (Original) A compound of claim 22, wherein R^1 is $C(O)R^3$.

25. (Original) A compound of claim 24, wherein R^3 is $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_1–C_8)$alkyl, aryl, or $(C_0–C_4)$alkyl–OR^5.

26. (Original) A compound of claim 25, wherein heteroaryl is pyridyl, furyl, or thienyl.

27. (Original) A compound of claim 22, wherein R^1 is $C(O)OR^4$.

28. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is ~~H,~~ $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1$-$C_4)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

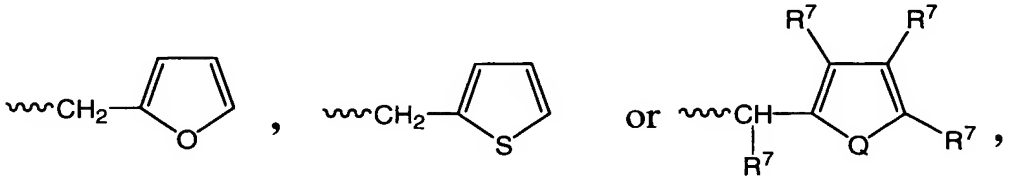
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–C(O)O–R^5 or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

29. (Original) A compound of claim 28, wherein R^1 is $(C_1–C_8)$alkyl, benzyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or



wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, halogen, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–C(O)OR^5, $(C_1–C_8)$alkyl–O(CO)R^5, or C(O)OR^5, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

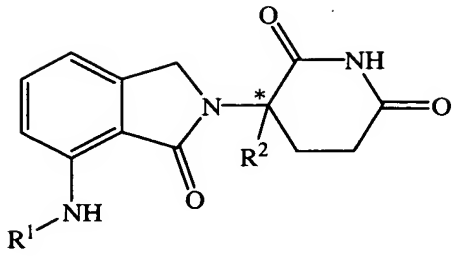
30. (Original) A compound of claim 28, wherein R^1 is C(O)R^3.

31. (Original) A compound of claim 30, wherein R^3 is $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_1–C_8)$alkyl, aryl, or $(C_0–C_4)$alkyl–OR^5.

32. (Original) A compound of claim 31, wherein heteroaryl is pyridyl, furyl, or thienyl.

33. (Original) A compound of claim 28, wherein R^1 is C(O)OR^4.

34. (Currently Amended) A compound having the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

R^1 is ~~H,~~ $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H or $(C_1$-$C_4)$alkyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

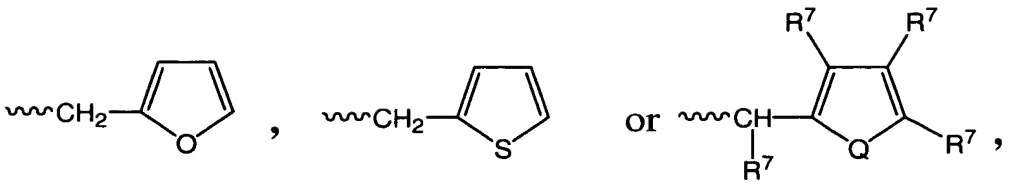
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

35. (Original) A compound of claim 34, wherein R^1 is $(C_1–C_8)$alkyl, benzyl, CH_2OCH_3, $CH_2CH_2OCH_3$, or



wherein Q is O or S, and each occurrence of R^7 is independently H,$(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, halogen, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

36. (Original) A compound of claim 34, wherein R^1 is $C(O)R^3$.

37. (Original) A compound of claim 36, wherein R^3 is $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_1–C_8)$alkyl, aryl, or $(C_0–C_4)$alkyl–OR^5.

38. (Original) A compound of claim 37, wherein heteroaryl is pyridyl, furyl, or thienyl.

39. (Original) A compound of claim 34, wherein R^1 is $C(O)OR^4$.

40. Cancelled

41. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable vehicle or carrier.

42. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 10 and a pharmaceutically acceptable vehicle or carrier.

43. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 14 and a pharmaceutically acceptable vehicle or carrier.

44. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 18 and a pharmaceutically acceptable vehicle or carrier.

45. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 22 and a pharmaceutically acceptable vehicle or carrier.

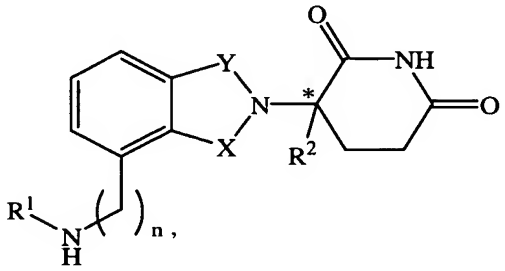
46. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 28 and a pharmaceutically acceptable vehicle or carrier.

47. (Original) A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 34 and a pharmaceutically acceptable vehicle or carrier.

48. Cancelled.

49. (Original) A method of modulating the production of TNF-α in a mammal comprising administering to said mammal an effective amount of a compound of claim 1.

50. (Currently Amended) A method of modulating the production of IL-1β in a mammal comprising administering to said mammal an effective amount of a compound of the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

one of X and Y is C=O and the other is CH_2 or C=O;

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H, F, benzyl, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$alkynyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

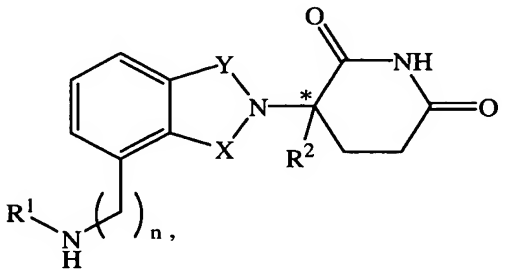
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R^1 is not H.

51. (Currently Amended) A method of modulating the production of IL-10 in a mammal comprising administering to said mammal an effective amount of a compound of the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

one of X and Y is C=O and the other is CH_2 or C=O;

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H, F, benzyl, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$alkynyl;

R^3 and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

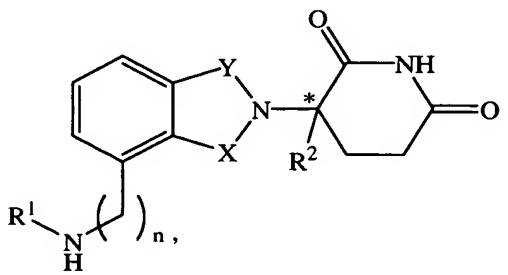
R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0$-$C_8)$alkyl–C(O)O–R^5 or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R^1 is not H.

52. (Currently Amended) A method of modulating the production or proliferation of T-cells in a mammal comprising administering to said mammal an effective amount of a compound of the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

one of X and Y is C=O and the other is CH_2 or C=O;

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H, F, benzyl, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, or $(C_2–C_8)$alkynyl;

R^3 and $R^{3'}$ are independently $(C_1$-$C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R^1 is not H.

53-56. Cancelled.

57. (Original) A method of treating cancer in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1 and another chemotherapeutic agent.

58. (Original) The method of claim 57, wherein the other cancer chemotherapeutic agent is paclitaxel, cisplatin, tamoxifen, docetaxel, epirubicin, doxorubicin, irinotecan, leuprolide, bicalutamide, goserelin implant, gemcitabine, or sargramostim.

59. (Original) The method of claim 57, wherein the other cancer chemotherapeutic agent is an anti-cancer vaccine.

60. (Original) A method of treating an inflammatory disorder in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

61. (Original) The method of claim 60, wherein the inflammatory disorder is arthritis, rheumatoid spondylitis, psoriasis, inflammatory bowel disease, post ischemic perfusion injury, or chronic inflammatory pulmonary disease.

62. (Original) The method of claim 61, wherein the arthritis is rheumatoid arthritis or osteoarthritis.

63. (Original) A method of treating heart disease in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

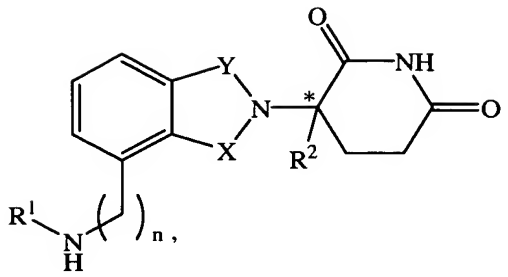
64. (Original) A method of modulating-the production of TNF-α in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

65. (Original) A method of modulating-the production of IL-1β in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

66. (Original) A method of modulating-the production of IL-10 in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

67. (Original) A method of modulating the production of T-cells in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

68. (Currently Amended) A method of modulating the production of cytokines in a mammal comprising administering to said mammal an effective amount of a compound of the formula:



~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof,~~ wherein:

one of X and Y is C=O and the other is CH_2 or C=O;

R^1 is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

R^2 is H, F, benzyl, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, or $(C_2–C_8)$alkynyl;

R^3 and $R^{3'}$ are independently $(C_1$-$C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–OR^5, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

R^4 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–OR^5, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

R^5 is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of R^6 is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R^1 is not H.

69. (Previously Presented) The method of claim 68 wherein the cytokine is IL-2.

70. (Previously Presented) The method of claim 68 wherein the cytokine is interferon-γ.

71. (New) A compound wherein the compound is:

(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid *tert*-butyl ester;

N-{(2-(2,6-dioxo(3-piperidyl)-1,3-dioxoisoindolin-4-yl)methyl}cyclopropyl-carboxamide;

(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid ethyl ester;

2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid benzyl ester;

1-*tert*-butyl-3-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-urea;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-3,3-dimethylbutanamide;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-2-methoxyacetamide;

(*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}carbamoyl)methyl acetate;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}(ethylamino)carboxamide;

methyl {*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)carbamoyl}formate;

N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}(cyclopentylamino)carboxamide;

N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}(3-pyridylamino)carboxamide Hydrochloride; or

N-{[2,(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}piperidylcarboxamide.

72. (New) A compound wherein the compound is:

4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione;

N-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4ylmethyl)-acetamide;

2-chloro-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}acetamide;

2-azido-N-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl-methyl)-acetamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)propanamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-chloroacetamide;

2-azido-*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)acetamide;

N-(2-(2,6-dioxo(3-piperidyl))-1-oxoisoindolin-4-yl)-2-chloroacetamide; or

2-azido-*N*-(2-(2,6-dioxo(3-piperidyl))-1-oxoisoindolin-4-yl)acetamide.

73. (New) A compound wherein the compound is:

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-3-pyridylcarboxamide;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}propanamide;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-3-pyridylcarboxamide;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-2-thienylcarboxamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-phenylacetamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-pyridylcarboxamide;

2-benzyloxy-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;

Tert-Butyl 4-(N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}(carbamoyl)piperazinecarboxylate;

N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}(diethylamino)carboxamide;

Cyclopropyl-N-{[2-(3-methyl-2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}carboxamide;

N-{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisoindolin-4-yl]methyl}cyclopropylcarboxamide;

N-{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisoindolin-4-yl]methyl}(ethylamino)carboxamide; or

Piperazine-1-carboxylic acid [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-amide .

74. (New) A compound wherein the compound is:

3-{1-oxo-4-(benzylamino)isoindolin-2-yl}piperidine-2,6-dione;

2-(2,6-dioxo(3-piperidyl))-4-(benzylamino)isoindoline-1,3-dione;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}heptanamide;

N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-2-furylcarboxamide;

ethyl 6-(*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}carbamoyl)hexanoate;

3-((*tert*-butoxy)carbonylamino)-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}propanamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)heptanamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)pentanamide;

methyl 3-{*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)carbamoyl}propanoate;

3-(1-oxo-4-(pentylamino)isoindolin-2-yl)piperidine-2,6-dione;

2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione;

2-(2,6-dioxo-piperidin-3-yl)-4-pentylamino-isoindole-1,3-dione;

2-(2,6-dioxo-piperidin-3-yl)-4-heptylamino-isoindole-1,3-dione;

4-(3-Chloro-benzylamino)-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;or

3-[4-(3-Chloro-benzylamino)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione.

75. (New) A compound wherein the compound is:

2-(2,6-Dioxo(3-piperidyl))-4-[(2-furylmethyl)amino]isoindoline-1,3-dione

{N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)carbamoyl}methyl acetate;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-thienylcarboxamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-furylcarboxamide;

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)benzamide;

3-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-phenoxy-acetamide;

4-(2-benzyloxy-ethylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methyl-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-trifluoromethyl-benzamide;

4-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;

cyclopropanecarboxylic acid [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-fluoro-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-trifluoromethyl-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methyl-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-nitro-benzamide;

5-{[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylamino]-methyl}-furan-2-carboxylic acid;

4-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione; or

4-[(Benzofuran-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione.

76. (New) A compound wherein the compound is:

7-amino-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}heptanamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}butanamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}benzamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}phenylacetamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}-2-pyridylcarboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}undecamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}-2-methylpropanamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}cyclopentylcarboxamide; or

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}cyclohexylcarboxamide.

77. (New) A compound wherein the compound is:

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-ethoxy-acetamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylsulfanyl-acetamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methoxy-benzamide; or

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-fluoro-benzamide.

78. (New) A compound wherein the compound is:

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(phenylamino)carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(butylamino)carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(propylamino)carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(cyclohexylamino)carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}[(methylethylamino)]carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(octylamino)carboxamide;

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(benzylamino)carboxamide; or

N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl] methyl}(cyclopropylamino)carboxamide.

79. (New) A compound wherein the compound is:

2-(2,6-dioxo-piperidin-3-yl)-4-{[(furan-2-ylmethyl)-amino]-methyl}-isoindole-1,3-dione;

N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;

2-dimethylamino-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methyl-benzamide;

Heptanoic acid[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-dihydro-1H-isoindol-4-yl]-amide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3,3-dimethyl-butyramide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-isobutyramide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-phenyl-propionamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methoxy-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-trifluoromethyl-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-malonamic acid methyl ester;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-propionamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-hydroxy-acetamide

4-[(furan-2-ylmethyl)-amino]-2-(1-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;

2-(2,6-Dioxo(3-piperidyl))-4-({[(cyclohexylamino)thioxomethyl]amino} methyl)isoindole-1,3-dione;

2-(2,6-Dioxo(3-piperidyl))-4-({[(ethylamino)thioxomethyl]amino} methyl)isoindole-1,3-dione;

2-(2,6-Dioxo(3-piperidyl))-4-({[(propylamino)thioxomethyl]amino} methyl)isoindole-1,3-dione;

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]-2-chloro-benzylamine;

{5-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylcarbamoyl]-pentyl}-carbamic acid benzyl ester;

2-Methoxy-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;

Pentanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide; or

Heptanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide.

80. (New) A compound wherein the compound is:

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-isonicotinamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-acetamide; or

{5-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylcarbamoyl]-pentyl}-carbamic acid benzyl ester.

81. (New) A compound wherein the compound is:

2-(dimethylamino)-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}-acetamide; or

N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)-2-methoxyacetamide.

82. (New) A compound wherein the compound is:

2-amino-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}acetamide;

3-amino-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}propanamide; or

ethyl 2-((N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl)methyl}carbamoyl) amino)acetate.

83. (New) A compound wherein the compound is:

2-amino-*N*-(2-(2,6-dioxo(3-piperidyl))-1-oxoisoindolin-4-yl)acetamide;

3-{4-((2-furylmethyl)amino)-1-oxoisoindolin-2-yl}piperidine-2,6-dione;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-nitro-benzamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-butyramide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylamino-acetamide;

2-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;

[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-carbamic acid benzyl ester;

N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;

Pentanoic acid [2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-amide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-propionamide;

N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-nicotinamide;

3-Chloro-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;

N-[2-(3-Methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-propionamide;

Thiophene-2-carboxylic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide;

2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-methyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione;

2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-hydroxymethyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione;

2-(2,6-Dioxo-piperidin-3-yl)-4-[(thiophen-2-ylmethyl)-amino]-isoindole-1,3-dione;

4-(3-Chloro-benzylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione; or

2-(2,6-Dioxo-piperidin-3-yl)-4-[(pyridin-3-ylmethyl)-amino]-isoindole-1,3-dione.

84. (New) A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 71-83 and a pharmaceutically acceptable vehicle or carrier.

85. (New) A method of treating cancer in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1, 10, 14, 18, 22, 28, 34, or 71-83.

86. (New) The method of claim 85, wherein the cancer is a solid tumor or a blood born tumor.

87. (New) The method of claim 85, wherein the cancer is cancer of the skin, blood, lymph node, breast, cervix, uterus, gastrointestinal tract, lung, ovary, prostate, mouth, brain, head, neck, throat, colon, rectum, testes, kidney, pancreas, bone, spleen, liver, bladder, larynx, or nasal passages.

88. (New) The method of claim 85, wherein the cancer is melanoma, multiple myeloma, or a leukemia.

89. (New) A pharmaceutically acceptable salt of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83.

90. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a pharmaceutically acceptable salt.

91. (New) A pharmaceutically acceptable solvate of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83.

92. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a pharmaceutically acceptable solvate.

93. (New) A pharmaceutically acceptable hydrate of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83.

94. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a pharmaceutically acceptable hydrate.

95. (New) A clathrate of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83.

96. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a clathrate.

97. (New) A stereoisomer of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83.

98. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a stereoisomer.

99. (New) A racemate of a compound of any one of claims 1, 10, 14, 18, 22, 28, 34 or 71-83 wherein the compound is a racemate.

100. (New) The method of any one of claims 50, 51, 52 or 68, wherein the compound is a racemate.

REMARKS

Upon entry of the present amendments, claims 1-39, 41-47, 49-52, and 56-100 are pending in this application. Claims 22, 28 and 34 have been amended to recite that R^2 is H or $(C_1\text{-}C_4)$alkyl. Support for this amendment can be found throughout the specification and in the claims as originally filed. Claims 2 and 3 have been amended to recite "the substantially pure R-form" and "the substantially pure S-form" respectively. Support for this amendment can be found, for example, at page 19, lines 25-35. Applicants respectfully point out that the terms $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_5)$heteroaryl, and $(C_1\text{-}C_6)$heterocycloalkyl as used in the claims are expressly defined in the specification at pages 24-26. Subject matter from claims 1, 10, 14, 18, 22, 28, 34, 50, 51, 52 and 68 have been set forth in new claims 71-97. In particular, new claims 71-84 relate to compounds and pharmaceutical compositions described in the specification and in original claim 40 and 48; new claims 85-88 relate to a method of treating cancer in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of the invention; 89 and 90 relate to pharmaceutically acceptable salts; 91 and 92 relate to pharmaceutically acceptable solvates; 93 and 94 relate to pharmaceutically acceptable hydrates ; 95 and 96 relate to clathrates; 97 and 98 relate to stereoisomers; and 99 and 100 relate to racemates. Support for these claims can be found throughout the specification and in the claims as originally filed. No new matter has been added. Applicants reserve their rights to prosecute the subject matter of any canceled claim or any otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

On page 2 of the Final Office Action, claims 49-55, 57-59, 63-67 and 68-70 are rejected under 35 U.S.C. § 112 first paragraph, as allegedly not enabled. Applicants respectfully disagree this rejection for the following reasons.

As the Examiner is aware, patents preferably omit what is well known in the art. Manual of Patent Examining Procedure ("M.P.E.P"), § 2164.01 (8th *ed.*, August 2001). Consequently, "the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Id.* (quoting *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Furthermore, experimentation is not "undue" simply because it may be complex, expensive, or time-consuming. *Id.*, §§ 2164.01 and 2164.06 (citing, *for*

example, In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)).

Claims 49-52 and 64-67 are directed, in part, to methods of modulating the production of certain cytokines and T-cells. As Applicants have repeatedly pointed out, "modulation" is a term well-known in the art.[1] *See, e.g., Stedman's Medical Dictionary* (26th Ed.), page 1122 (attached hereto as Exhibit A). Unlike the definition asserted by the Examiner, it does not requite the simultaneous enhancement and inhibition of an activity by a single compound. It also does not mean that the compound "neither enhances nor inhibits" any activity, as suggested by the Examiner. Modulation does ***not*** mean "merely administered." (*See*, Final Office Action, Page 2).

According to the methods of claims 49-52 and 64-67, modulation is achieved by administering a compound of the invention to a mammal, or by contacting mammalian cells or mammalian tissue with a compound of the invention. This modulation can be readily accomplished by those of ordinary skill in the art, as Applicants have fully described methods of administering compounds of the invention. (*See e.g.*, page 80, line 1 through page 84, line 23). Applicants have also fully described how to synthesize compounds of the invention. (*See e.g.*, page 70 line 1 through page 77, line 33). Applicants have further described assays that can be used to determine the biological activity of compounds of the invention, and other means of testing the compounds to modulate TNF-α, IL-1β, IL-10 or T-cell production are well known to those of ordinary skill in the art. (*See, e.g.*, p. 86-88). Thus, one of ordinary skill in the art would be readily able to determine if a compound modulates TNF-α, IL-1β, IL-10 or T-cell production, and would easily be able to make and use the claimed invention with no or merely routine experimentation. *See, In re Wands,* 858 F.2d 731 (Fed. Cir. 1988).

Turning to claims 53-55, 57-59, and 63, Applicants respectfully submit that the claims are directed to the use of clearly defined compounds, for which methods of preparation, routes of administration and amounts are set forth in the specification as filed. Moreover, the determination by a physician as to whether a recited compound is effective in treating a particular disease or disorder is a type of determination that is always made by

[1] On page 2 of the Final Office Action, the examiner states that "Applicants have been given citations from the art to understand the ordinary level of understanding in this particular art," and implies that Applicants have provided no factual evidence supporting this point. On the contrary, the cited references <u>are</u> evidence of what the term "modulate" means.

physicians for every pharmaceutical. Indeed, the determination is a routine one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the full scope of the inventions of claims 53-55, 57-59, and 63 without undue experimentation.

More important, Applicants remind the Examiner that the Patent Office cannot require evidence of enablement above and beyond that which is acceptable to the skilled artisan. *In re Brana* 51 F. 3d 1560 (Fed. Cir. 1998). Because the specification provides information and data to enable those of ordinary skill in the art to practice the claimed invention, the Examiner cannot require more, such as clinical data. *See, Id.*

In sum, because no evidence to the contrary has been cited, Applicants respectfully request that the rejection of claims 49-55, 57-59, 63-70 be withdrawn.

The Rejection Under 35 U.S.C. § 102(b) Should be Withdrawn

On Page 2 of the Final Office Action, claims 1, 4, 6, 9, 12, 22, 24, 25, 28, 30, 34, 36, 37 and 40 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by International Patent Publication WO 98/54170 to Muller et al. ("Muller"). Applicants respectfully traverse this rejection for the following reasons.

A prior art reference must disclose all of the limitations of a claim in order to anticipate that claim. M.P.E.P. § 2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Put another way, "[a] claim is anticipated and therefore invalid only when a single prior art reference discloses *each and every* limitation of the claim." *Glaxo Inc. v. Novapharm Ltd.*, 52 F.3d 1043, 1047, cert. denied, 116 S. Ct. 516 (1995) (citations omitted) (emphasis added).

Applicants' claim 1 recites that when n is 0, R^1 is not H. R^1 is H in all species disclosed in Muller; namely, those compounds in Examples 12-14 relied upon by the Examiner as allegedly anticipatory. Similarly, R^1 is not H in claims 22, 24, 25, 28, 30, 34, 36 or 37. Consequently, the claims do not encompass the species disclosed by Muller. Furthermore, Formula IIB of Muller requires that the -NHR^5 moiety be bound directly to the benzene functionality. (*See, e.g.,* Muller page 10, lines 3-24). The compounds of claim 1, when n is not 0, all have at least a methylene group between the benzene functionality and the-NHR moiety. Similarly, the compounds of claim 12 all have a methylene linker between benzene functionality and the -NHR moiety. Therefore, the rejection should be withdrawn.

Claims 22, 28, and 34 have previously been amended to remove their dependency on claim 1. Claims 1, 22, 24, 25, 28, 30, 34 and 36 do not read on Formula IIB of Muller. Formula IIB discloses, *inter alia*, compounds where R^6 is alkyl of 1 to 8 carbon atoms, benzo, chloro or fluoro. (*See, e.g.*, Muller page 10, line 16). Claim 1, when n is 0, and claims 22, 24, 25, 28, 30, 34, 36, and 37, recite compounds where R^2 is hydrogen or (C_1-C_4)alkyl. Therefore, Muller (a) does not disclose all of the limitations of claims 1, 22, 24, 25, 28, 30, 34, 36, and 37, and (b) does not anticipate the instant claims.

Finally, claim 40 has previously been amended to remove its dependency on claim 1. Muller does not anticipate instant Claim 40 or any of new claims 71-84 which are based on now canceled claim 40. Applicants therefore respectfully request the rejections under 35 U.S.C. §102(b) be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 1-67 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over United States Patent No. 5,635,517 ("the '517 patent") in view of Muller, *Design of Prodrugs* by Hans Bundgaard ("Bungaard"), Naik CA 118 ("Naik") and WO 97/45117 to Smith et al. ("Smith"). Applicants respectfully traverse the rejection for the reasons discussed below.

In order to properly determine a *prima facie* case of obviousness, an examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P. §2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.* Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. *Id.* at § 2143. With regard to the first criterion, it is important to recognize that the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id.* at 2143.01 (citing *In re Mills*, 916 F.3d 680 (Fed. Cir. 1990)).

Claims 1-100 relate, *inter alia*, to compounds, compositions and methods of treatment using a novel class of isoindole-imide compounds. The '517 patent relates, *inter alia,* to a distinct class of isoindole-imide compounds. In fact, the Examiner has admitted that the compounds of the '517 patent are not encompassed by the present application. (*See,*

Final Office Action, page 3). The Examiner alleges, however, that the claimed compounds are prodrugs of compounds of the '517 patent or the compounds of Muller, and that the preparation of prodrugs is well known in the art as evidenced by Bungaard, Naik and Smith. The Examiner also alleges that the compounds of the present invention are prodrugs of thalidomide, and that one of skill in the art would be motivated to make a prodrug of thalidomide to avoid its adverse effects. Applicants respectfully disagree.

First, Applicants respectfully submit that the assertion that the presently claimed compounds are prodrugs of the compounds of the '517 patent or Muller is entirely without factual support (neither the art nor the instant specification refer to these compounds as prodrugs of thalidomide or any other molecule). To the extent these assertions are based on the Examiner's personal knowledge, Applicants respectfully request that such knowledge be supported by an affidavit. 37 C.F.R. §1.104(d)(2).

Second, while Bungaard does describe the formation of prodrugs generally, it teaches away from the use of N-Acyl derivatives "due to the relative stability of amides in vivo." (*See, e.g.*, Page 27). Indeed, Bungaard goes on to describe certain N-Acyl derivatives of a number of compounds unrelated to either the '517 patent or the present claims, most of which showed very rapid hydrolization and cleavage and "very limited solution stability." (*See, e.g.*, Page 29).

Neither Naik nor Smith does anything to rectify the deficiencies of the '517 patent alone or in combination with Bungaard. Naik describes specific prodrugs of ***azidoprofen*** esters.[2] (*See*, Abstract). Similarly, Smith teaches away from the compounds of the invention by describing ***dipeptide*** bound "prodrugs" of thalidomide. (*See, e.g.*, page 4, lines 15-19). Neither Naik nor Smith suggest the compounds of the claimed invention.

The Examiner has not demonstrated that the '517 patent alone or in combination with Muller, Bungaard, Naik or Smith suggests modifying the compounds of the '517 patent in the specific manner necessary to obtain the compounds of the invention. See, *In re Grabiack* 769 F. 2d 729 (Fed. Cir. 1985). In addition, the Examiner has not demonstrated that it would have provided those of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if such modification was suggested. *See In re Fine,* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

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[2] Applicants point out that it is improper for the Examiner to rely on an abstract. Indeed, the full paper must be considered. *Ex parte Gavin* 62 U.S.P.Q.2d 1680 (Bd. Pat. App. & Int'f 2001). Thus, the full paper us submitted herewith and a PTO-1449 form for evidence of consideration by the Examiner.

Moreover, none of the cited references provide any indication that modification of the compounds of the '517 patent would be effective in modulating the production of TNF-α, IL-1β, IL-10, IL-2, or T-cells in treating cancer, inflammatory disorders, or heart disease.

In sum, the Examiner has not demonstrated that the cited references disclose or suggest all of the limitations of the pending claims provide any motivation to obtain the claimed invention. As discussed above, Bungaad, Naik, and Smith actually teach away from the claimed invention. Consequently, Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. § 103.

The Obvious-Type Double Patenting Rejection Should be Withdrawn

On page 4 of the Office Action, claims 1-67 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-2 of United States Patent No. 6,395,754 ("the '754" patent) and over claims 1-10 of United States Patent No. 5,635,517 and claims 1-12 of United States Patent No 6,395,754 in view of Bungaard, Naik and Smith. As discussed above, the Examiner has not demonstrated that the cited references render the present invention obvious. Consequently, Applicants respectfully request that the obvious-type double patent rejections be withdrawn.

The Provisional Double Patenting Rejection Should be Withdrawn

On page 5 of the Office Action, claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-116 of co-pending United States Patent Application No. 09/972,487. This is a provisional rejection. Consequently, and without conceding to the appropriateness of the rejection, if the Examiner maintains this rejection when the claims are otherwise deemed allowable, Applicants will take the necessary steps to overcome it (*e.g.*, by filing a Terminal Disclaimer).